REMARKS

In view of the substance of the interview of February 8, 2005 the Applicant herein particularly points out the distinction of "directly monitoring" a PCR reaction in "real time" in contrast to the disclosure of Van Ness, *et al.*,'893.[1]

Claims 1, 4-7, 9-10, 12-14, and 45 are pending. The Applicants kindly thank the Examiner for the interview and herein respectfully requests further examination of the application and reconsideration of the claims, in view of the amendments and remarks presented herewith.

The Applicant understands that the only remaining issue, in view of the substance of the interview of February 8, 2005, is whether the subject matter of the instant claims now pending is anticipated under 35 USC §102(b) by the disclosure of Van Ness, *et al.*,'893.

The Examiner's position is that Van Ness specifically states "real time" monitoring using an interface, some of which are illustrated in FIG.15-16. The Examiner stated that the claimed invention is not distinct from that disclosed by Van Ness.

The Applicant respectfully highlights the Van Ness language relied upon by the Examiner:

> It will be evident to one in the art that a device (an interface) may be interposed between the separation and detection steps to permit the continuous operation of size separation and tag detection (in real time). This unites the separation methodology and instrumentation with the detection methodology and instrumentation forming a single device. For example, **an interface is interposed between a separation technique and detection** by mass spectrometry or potentiostatic amperometry.
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> The function of the interface is primarily the release of the (e.g., mass spectrometry) tag from analyte. There are several representative implementations of the interface. The design of the interface is dependent on the choice of cleavable linkers. In the case of light or photo-cleavable linkers, an energy or photon source is required. In the

[1] In view of the substance of the interview of November 30, 2004, the Applicants herein again respectfully request non-entry of the Amendment filed October 29, 2004.

> case of an acid-labile linker, a base-labile linker, or a disulfide linker, reagent addition is required within the interface. In the case of heat-labile linkers, an energy heat source is required. Enzyme addition is required for an enzyme-sensitive linker such as a specific protease and a peptide linker, a nuclease and a DNA or RNA linker, a glycosylase, HRP or phosphatase and a linker which is unstable after cleavage (e.g., similar to chemiluminescent substrates). Other characteristics of the interface include minimal band broadening, separation of DNA from tags before injection into a mass spectrometer. **Separation techniques include those based on electrophoretic methods and techniques, affinity techniques, size retention (dialysis), filtration and the like.**
>
> It is also possible to concentrate the tags (or nucleic acid-linker-tag construct), capture electrophoretically, and then release into alternate reagent stream which is compatible with the particular type of ionization method selected. The interface may also be capable of capturing the tags (or nucleic acid-linker-tag construct) on microbeads, shooting the bead(s) into chamber and then performing laser desorption/vaporization. Also it is possible to extract in flow into alternate buffer (e.g., from capillary electrophoresis buffer into hydrophobic buffer across a permeable membrane). It may also be desirable in some uses to deliver tags into the mass spectrometer intermittently which would comprise a further function of the interface. Another function of the interface is to deliver tags from multiple columns into a mass spectrometer, with a rotating time slot for each column. Also. it is possible to deliver tags from a single column into multiple MS detectors, separated by time, collect each set of tags for a few milliseconds, and then deliver to a mass spectrometer.

'893 disclosure at the top of Col. 64. Emphasis added.

The Applicant respectfully point out that the Van Ness '893 disclosure provides a method for sequencing nucleic acids that fundamentally and necessarily requires, in the order, 1) separation of nucleic acid fragments according to size, 2) cleavage of a tag from the nucleic acid, and 3) detection of the tag. "Following separation of the tagged fragments by sequential length, the tags are cleaved from the tagged fragments. In a preferred embodiment, the tags are detected by mass spectrometry and the sequence of the nucleic acid molecule is determined therefrom." *See*, Van Ness' Abstract of the Disclosure. The is requirement is unequivocally illustrated globally throughout the specification as well as in Van Ness' FIG.15-16 highlighted by the Examiner.

In sharp contrast, the Applicants disclosure, is exemplified as follows:

> [0035] The biotech, chemical, and pharmaceutical industries have been waiting for a technique to use the direct detection and monitoring of biomolecular mechanisms (e.g., amplification reaction of PCR products) without radioisotopic labeling or photolabeling (i.e., fluorescence or chemiluminescence). The present invention relates to a method and apparatus for detecting preferably a biomolecule as it undergoes an amplification reaction.
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> [0064] A preferred embodiment of the invention involves the detection and/or analysis of nucleotides and polynucleotides. The nucleotides and polynucleotides can be either directly and/or indirectly sampled. Direct sampling would detect the biomolecule or part of it. Indirect sampling methods include, but are not limited to, sampling the medium, sampling a tag on the nucleotide, sampling the headspace, and sampling the biomolecule itself.
>
> [0071] The invention relates generally to the *in-situ* monitoring of an amplification reaction of one or more biomolecules using a multisensor array (MSA) or at least one sensor with several possible physical and/or chemical responses for detecting some volatile compounds.

Since all subject matter of the instant claims now pending is limited to a method for ***directly*** monitoring a *polymerase chain reaction*, i.e. interrogating (probing) the medium *during* the reaction, without the express need for separation nucleic acids before detection, none of the claims presented herewith encompass anything within the disclosure of Van Ness '893.

The Applicant therefore respectfully request the Examiner to withdraw the rejection under 35 USC §102 in view of Van Ness '893.

Koster ('394) "Automated Process Line"

The Applicant respectfully remind the Examiner that anticipation, *per se*, under 35 USC §102 necessarily requires *that all of the limitations* of a pending claim must be disclosed in a single prior art reference. To anticipate a claim, the reference must teach every element of the claim.

"The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Koster, et al., is directed toward an automated process line for evaluating the results of a large amount of completed reactions pertaining to a large amount of different samples, i.e., "continuously processing reaction vessels one after another ... the APL [automated process line] can run unattended continuously with a continuous sample throughput and is capable of analyzing on the order of 10,000-50,000 genotypes per day." Koster, ¶10-11. The Examiner is particularly referred to Koster ¶65:

> **In steps where sample vessels are to be sealed, such as when subjected to PCR amplification**, or unsealed, such as for reagent addition or removal, an automated lid application/removal and sealing system may be integrated into the system. Examples of these include a lid parking station, such as is available from Robocon, and a plate sealer, such as the "MJ Microseal", available from MJ Research. A system turntable might also be employed to assist the system robot in orienting the samples for delivery into each station of the APL. Such a turntable is available, for example, from Robocon. Additionally, a shaker is also included in the APL system in embodiments where beads or other reagents are added to the sample for immobilizing the sample, or where other manipulations requiring mechanical shaking are involved. [Emphasis added]

The Examiner is also particularly referred to Koster ¶96:

> **After PCR amplification**, the plates are removed from the PCR reaction station 162 by the robot 150. The plates are then moved to the lid park station 158, where the lids are removed and **unsealed**. As noted above, however, a penetrable seal such as a foil wrap or parafilm is an alternative to a lid seal, and if removable lids are not used to seal the plates, then the lid park station is unnecessary and the next substance that must be added to the wells of the plate will be inserted upon piercing of the foil wrap. [Emphasis added]

Koster, however, does not teach or contemplate a method for directly monitoring volatile compounds in a gas or vapor phase medium from a polymerase chain reaction, during the reaction. Koster merely contemplate a system in abstract terms that can evaluate a solid-phase reaction by means of mass spectrometry, preferably ***after*** **the reaction is completed**. DNA sequencing using mass spectrometry . See, e.g., Koster paragraphs 82, 83, 96.

It is improper, in determining whether a person of ordinary skill would have been led to a solution to a problem, simply to "[use] that which the inventor taught against its teacher." W.L. Gore v. Garlock, Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983). Koster paragraphs 108-125, as cited by the Examiner, merely contemplate a system in abstract terms that can evaluate a solid-phase reaction by means of mass spectrometry. Koster, however, does not contemplate any embodiments that fall within the Applicant's claims now presented.

The Applicant, accordingly, respectfully requests the Examiner to withdraw the rejection.

Rejections under 35 USC §103

The subject matter of claims 4-6 and 45 is rejected as obvious in view of the disclosure of Van Ness ('893) combined with Freidhoff ('115) and Van Ness ('893) combined with Koster ('394), respectively.

The Applicant respectfully point out the necessary distinction of the polymerase chain reaction limitation of the amended claims presented herewith, i.e, *directly* monitoring volatile compounds in a gas or vapor phase medium *during* the reaction. The '893 disclosure provides a method for sequencing nucleic acids that fundamentally and necessarily requires, in the order, 1) separation of nucleic acid fragments according to size, 2) cleavage of a tag from the nucleic acid, and 3) detection of the tag. The method of the present invention, in sharp contrast, is drawn toward a method for directly monitoring volatile compounds in a gas or vapor phase medium from a polymerase chain reaction, *during* the reaction. This language patentably distinguishes now presented claims 4-6 and 45 to the instant invention.

The Applicant respectfully requests the Examiner to withdraw the rejections.

For all the foregoing reasons, the Applicant submits that Claims 1, 4-7, 9-10, 12-14, and 45 are in condition for allowance. Early action toward this end is courteously solicited.

The Commissioner is authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1943.

The Examiner is kindly encouraged to telephone the undersigned in order to expedite any detail of the prosecution.

Respectfully submitted,

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